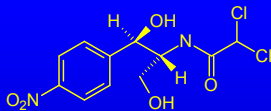


Developmental Pharmacology

Scaling adult doses to infants based on body weight or surface area does not account for developmental changes that affect drug disposition or tissue/organ sensitivity.

Frank Balis, M.D.
February 19, 2009

Chloramphenicol



- Natural product of *Streptomyces* (1947)
- Inhibits protein synthesis (bacteriostatic)
- Eliminated by glucuronide conjugation (90%) and renal excretion (<10%)
- Nursery infections treated with high doses

Chloramphenicol in Infants

- 3320 gm infant, 44 week gestation
- Meconium stained, foul smelling, timing of ROM unknown
- Procaine penicillin (50,000 units) + chloramphenicol (250 mg) IM q8h - 230 mg/kg/day x 72 hr
- Day 4, gray color & cold, moist skin
- Died at 106 hr, 8 hr after onset of vascular collapse

Sutherland, Am J Dis Child 97:761-7, 1959

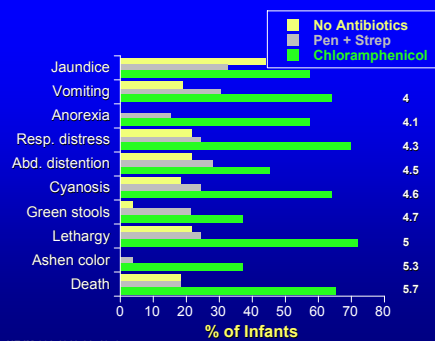
Chloramphenicol in Premature Infants

Premature infants born ≥ 24 hrs after ROM

	All Infants		2001-2500 gm	
	n	Deaths	n	Deaths
No antibiotics	32	6	17	1
Pen + strep	33	6	24	0
Chloramphenicol	30	19	16	8
Pen + strep + chloramphenicol	31	21	15	6

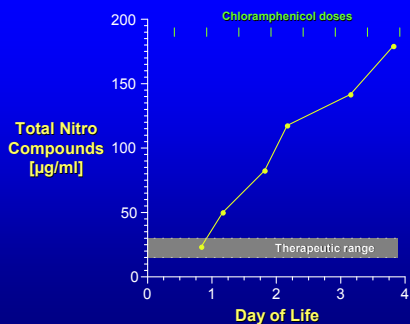
Burns et al., NEJM 261:1318-21, 1959

Gray Baby Syndrome



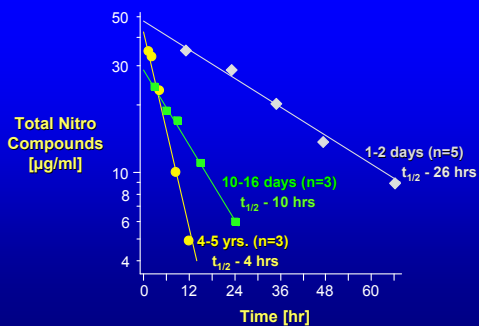
Burns et al., NEJM 261:1318-21, 1959

Chloramphenicol Blood Levels



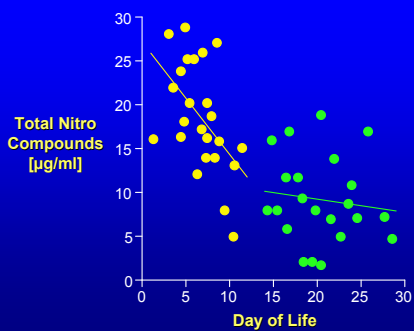
Burns et al., NEJM 261:1318-21, 1959

Chloramphenicol Pharmacokinetics



Weiss et al., NEJM 262:787-94, 1960

Repeated Administration



Weiss et al., NEJM 262:787-94, 1960

Drug Use in Infants and Children

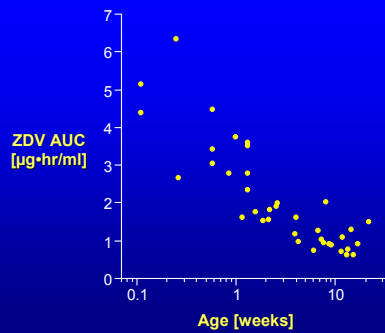
- Scaling adult doses based on body weight or surface area does not account for developmental changes that affect drug disposition or tissue/organ sensitivity.
- Pharmacologic impact of developmental changes are often discovered when unexpected or severe toxicity in infants and children leads to detailed pharmacologic studies.
- Therapeutic tragedies could be avoided by performing pediatric pharmacologic studies during the drug development process (before wide-spread use of agents in infants and children).

Zidovudine



- Synthetic nucleoside analog
- Inhibits HIV reverse transcriptase
- Eliminated by glucuronide conjugation (67%) and renal excretion (33%)
- Perinatal therapy to prevent HIV transmission

Zidovudine in the Newborn



Boucher et al., J Pediatr 122:137-44, 1993

Zidovudine in Newborns

Group	Age (days)	Clearance (ml/min/kg)	t _{1/2} (hr)	F (%)
Preterm	5.5	2.5	7.2	
	17.7	4.4	4.4	
Term	≥ 14	10.9	3.1	
	>14	19.0	1.9	

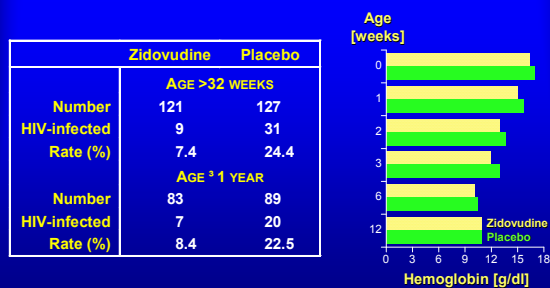
Age Group	Clearance (ml/min/kg)	t _{1/2} (hr)	F (%)
1-13 yrs	24	1.5	68
Adults	21	1.1	63

Boucher et al., J Pediatr 125:642-9, 1994
 Mirochnick et al., Antimicrob Agents Chemother 42:808-12, 1998
 Balis et al., J Pediatr 114:880-4, 1989
 Klecker et al., Clin Pharmacol Ther 41: 407-12, 1987

Prevention of Vertical Transmission

- Randomized, double-blind, placebo controlled trial
- Rate of vertical transmission was the primary endpoint
- Zidovudine/placebo regimen
 - Mothers: 100 mg of ZDV antepartum orally, 5 times daily, and then continuous infusion of 1 mg/kg/hr during labor and delivery
 - Infants: 2 mg/kg orally every 6 hours for 6 weeks, beginning 8-12 hours after birth.

Prevention of HIV Transmission



Connor et al., NEJM 331:1173-80, 1994

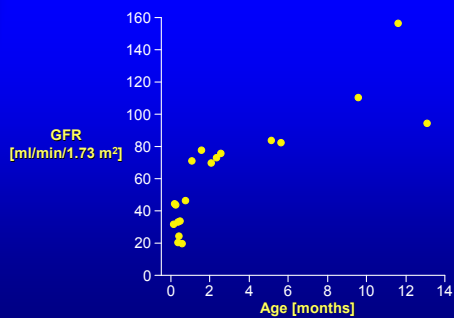
Ontogeny and Pharmacology

- Excretory organ (liver and kidneys) development has the greatest impact on drug disposition (pharmacokinetics)
- The most dramatic changes occur during the first days to months of life
- Anticipate age-related differences in drug disposition based on knowledge of ontogeny
- Effect of ontogeny on tissue/organ sensitivity to drugs (pharmacodynamics) is poorly studied
- Disease states may alter a drug's PK/PD

Renal Ontogeny

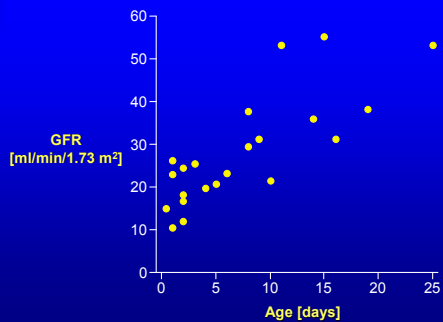
- **Glomerular filtration rate**
 - **Low at birth**
 - Full term newborn - 10-15 ml/min/m²
 - Premature - 5-10 ml/min/m²
 - GFR doubles by 1 week of age
 - Adult values by 6-12 months of age
- **Tubular function**
 - Secretory function impaired at birth
 - Glomerulotubular imbalance
 - Adult values by 1 year of age

Glomerular Filtration Rate

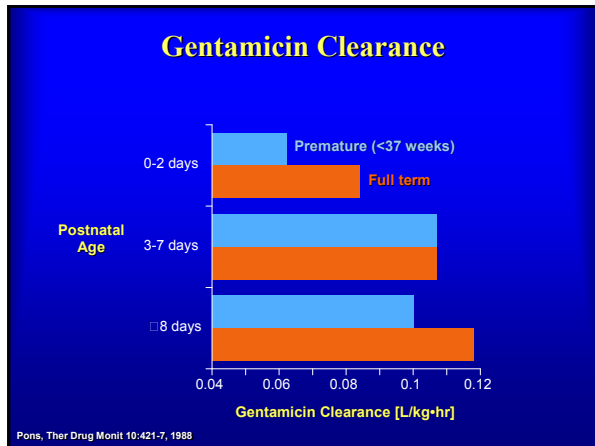


Aperia, Acta Paediatr Scand 64:393-8, 1975

GFR in Infants



Guignard, J Pediatr 87:268-72, 1975



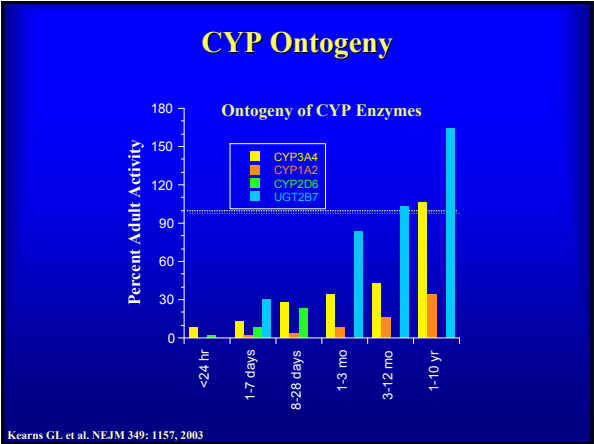
- ### Hepatic Ontogeny
- **Phase 1** (oxidation, hydrolysis, reduction, demethylation)
 - Activity low at birth
 - Mature at variable rates
 - Oxidative metabolism increases rapidly after birth
 - Alcohol dehydrogenase reaches adult levels at 5 yrs
 - Activity in young children exceeds adult levels
 - **Phase 2** (conjugation, acetylation, methylation)
 - **Conjugation:**
 - Glucuronidation ↓ at birth
 - Sulfatation ↑ at birth
 - Acetylation ↓ at birth, “fast” or “slow” phenotype by 12-15 mo.

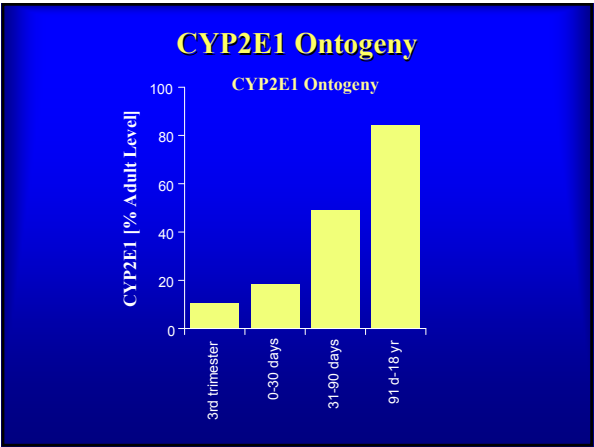
- ### Cytochrome P450 (CYP) Enzymes
- Superfamily of Phase 1 enzymes (oxidation, demethylation)
 - Nomenclature:

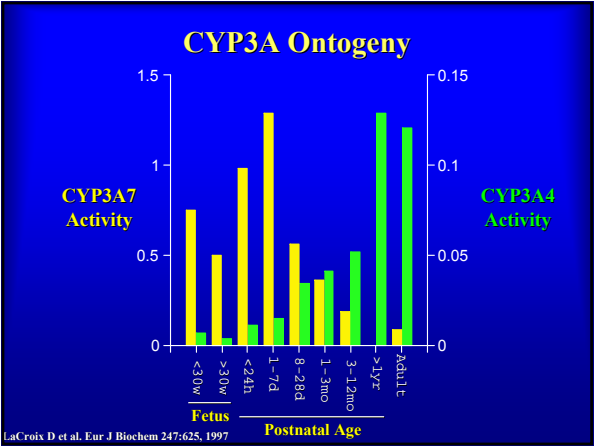
Family (>40%) ———┐ Subfamily (>55%)

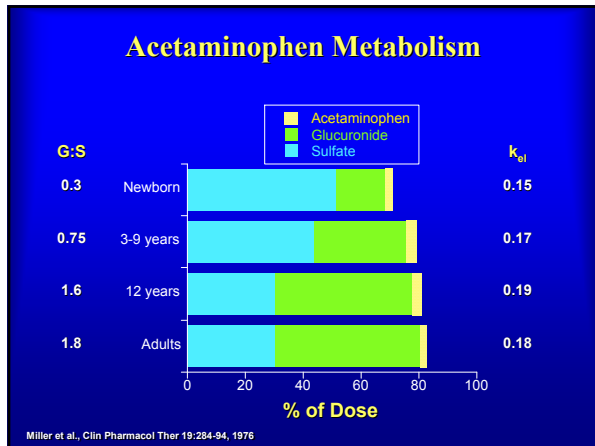
CYP3A4

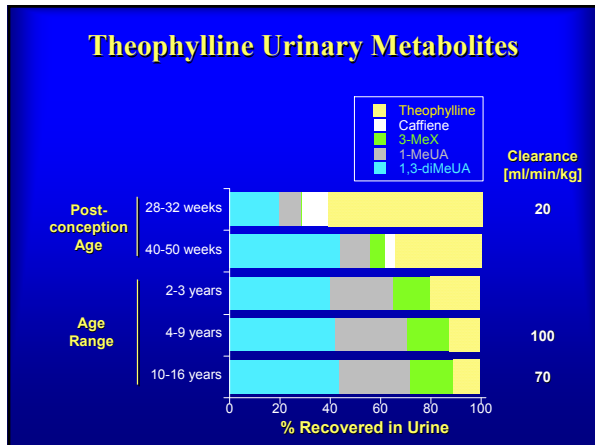
└ Isoform
 - 17 Families and 39 subfamilies in humans
 - CYP1, CYP2, CYP3 are primary drug metabolizing enzymes
 - Half of all drugs metabolized by CYP3A subfamily
 - CYP3A4 is most abundant hepatic P450 enzyme and metabolizes at least 50 drugs





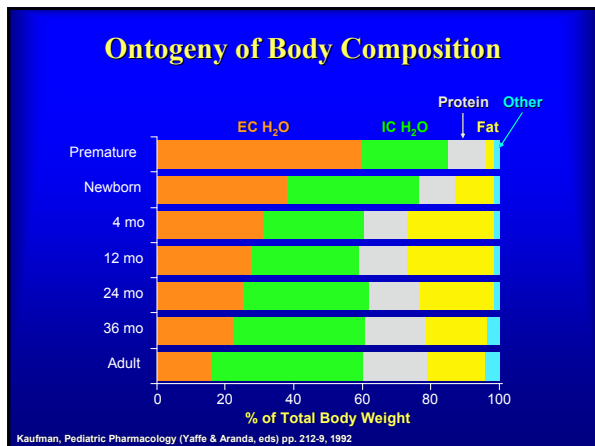


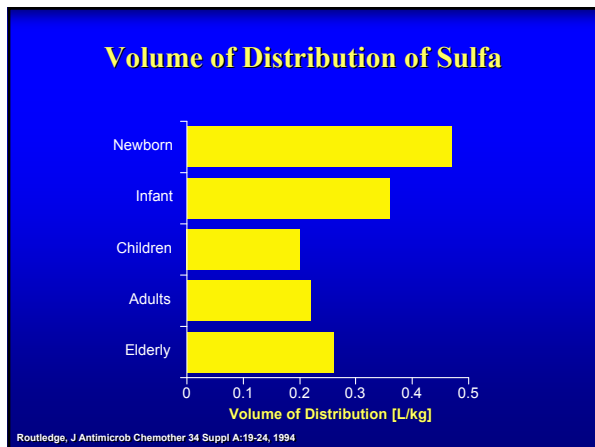




Factors Affecting Drug Distribution

- Physicochemical properties of the drug
- Cardiac output/Regional blood flow
- Degree of protein/tissue binding
- Body composition
 - Extracellular water
 - Adipose tissue





Tissue and Organ Weight

	% of Total Body Weight		
	Fetus	Newborn	Adult
Skeletal muscle	25	25	40
Skin	13	4	6
Skeleton	22	18	14
Heart	0.6	0.5	0.4
Liver	4	5	2
Kidneys	0.7	1	0.5
Brain	13	12	2

Plasma Proteins

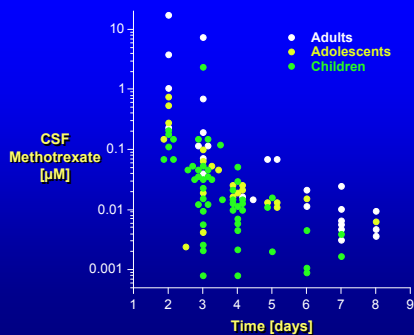
	Change from Adult Values		
	Newborn	Infant	Child
Total protein	↓	↓	=
Albumin	↓	=	=
α_1 -Acid glycoprotein	↓		=
Fetal albumin	Present	Absent	Absent
Globulin	↓	↓	=

Protein Binding in Cord and Adult Plasma

	Plasma Protein Binding (%)	
	Cord	Adult
Acetaminophen	36.8	47.5
Chloramphenicol	31	42
Morphine	46	66
Phenobarbital	32.4	50.7
Phenytoin	74.4	85.8
Promethazine	69.8	82.7
	30.2	17.3

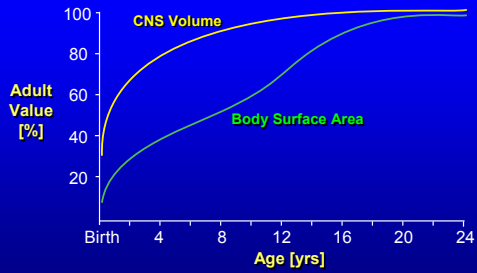
Kurz et al., Europ J Clin Pharmacol 11:463-7, 1977

CSF MTX and Age



Bleyer, Cancer Treat Rep 61:1419-25, 1977

CNS Growth and Development



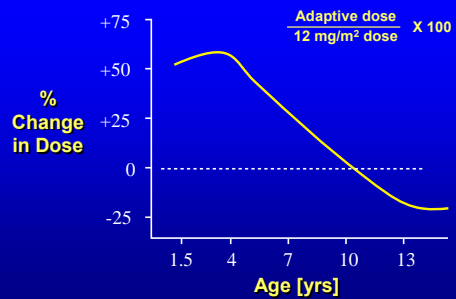
Bleyer, Cancer Treat Rep 61:1419-25, 1977

Adaptive IT MTX Dosing Regimen

AGE [YRS]	MTX DOSE [MG]
<1	6
1	8
2	10
≥ 3	12

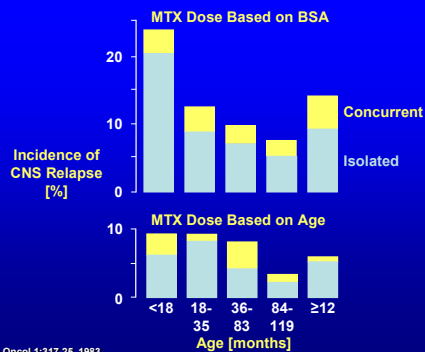
Bleyer, Cancer Treat Rep 61:1419-25, 1977

Dose Change with Adaptive Regimen



Bleyer, J Clin Oncol 1:317-25, 1983

Effect of Adaptive IT Dosing on Outcome



Bleyer, J Clin Oncol 1:317-25, 1983

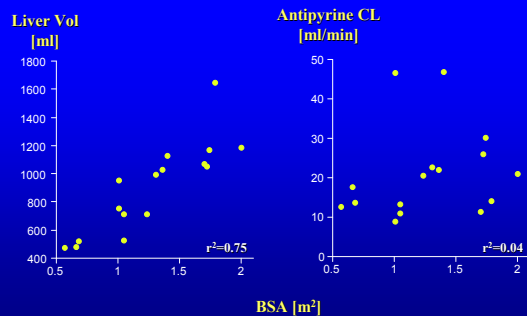
Dosing Based on Body Surface Area

- BSA = 2-dimensional surface area of the skin
- Estimated from formulas using weight & height
- Correlation between BSA and kidney/liver function is weak
- BSA dosing evolved from scaling doses from animals to humans (toxicology)

Species	Wt [kg]	BSA [m ²]	Dose [mg]	Dose [mg/kg]	Dose [mg/m ²]
Mouse	0.018	0.0075	0.027	1.5	3.6
Rat	0.25	0.045	0.125	0.5	2.8
Infant	8	0.4	1.25	0.15	3.1
Child	20	0.8	2.5	0.12	3.1
Adult	70	1.85	5.0	0.07	2.7

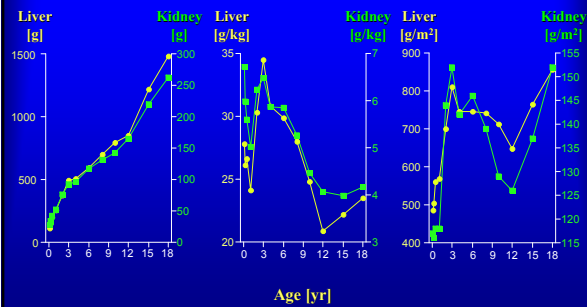
Pinkel, Cancer Res 18:853, 1958

Liver Function (Children)

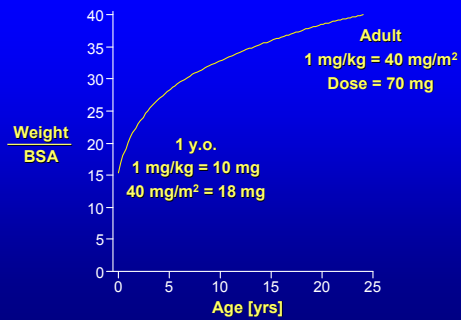


Murry et al. Drug Metab Disp 23:1110, 1995

Excretory Organ Growth



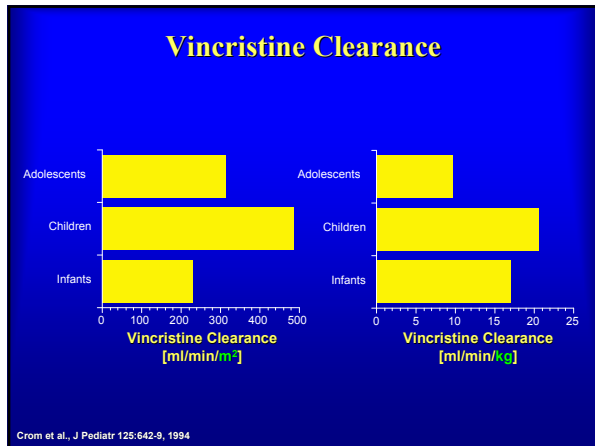
Body Weight:Surface Area

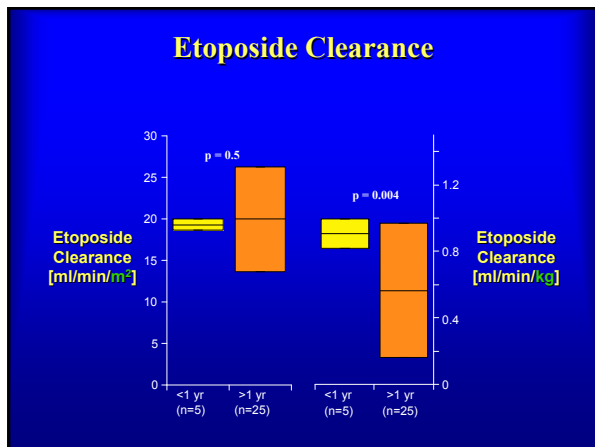


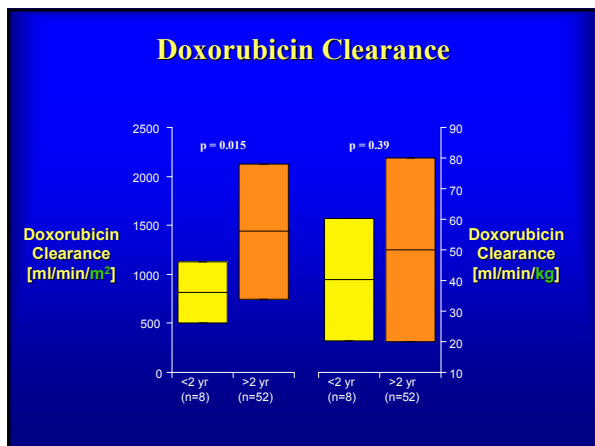
Anticancer Drug Clearance

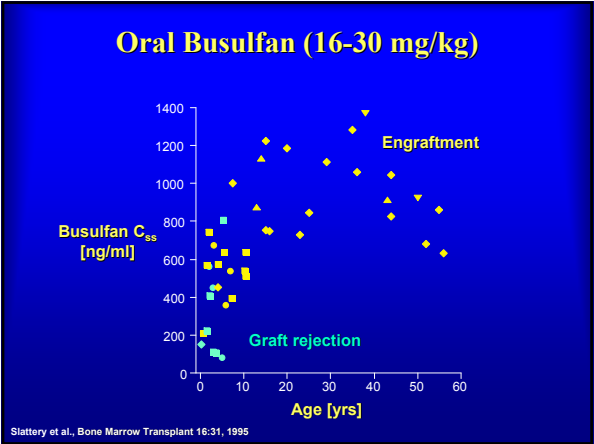
DRUG	ROUTE OF ELIMINATION	CL _{INFANTS} VS CL _{CHILDREN}	DOSING
Methotrexate	R	↓ (15%)	No adjustments
Mercaptopurine	M	ND	No adjustments
Vincristine	M	↓ (/m ²)	<1 yo, dose/kg
VM26/VP16	M	ND (/m ²)	No adjustments (/m ²)
Doxorubicin	B, M	↓ (/m ²)	<2 yo, dose/kg or ↓ dose/m ²
Cytarabine	M	ND	No adjustment

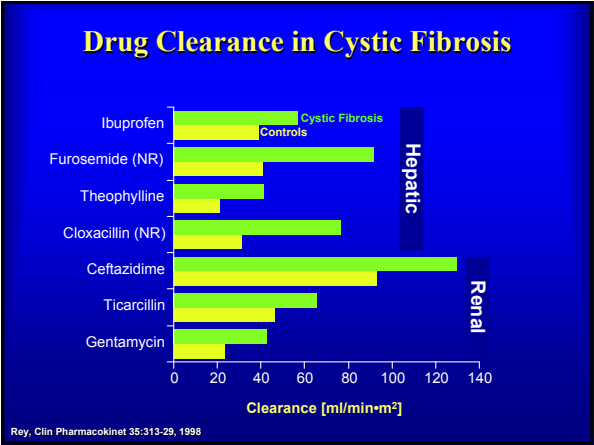
McLeod et al., Br J Cancer 66 (Suppl. 18):S23-S29, 1992









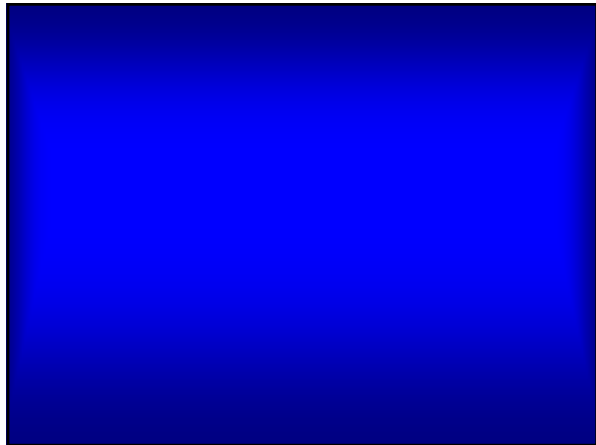


Retinoids

	≤12 Yr.	>12 Yr	Adult
ATRA			
MTD	60 mg/m ² /d	90 mg/m ² /d	150 mg/m ² /d
DLT	Pseudotumor cerebri	HA and PC	Dermatologic
9-cis-RA			
MTD	35 mg/m ² /d	85 mg/m ² /d	140 mg/m ² /d
DLT	Pseudotumor cerebri	HA and PC	HA, diarrhea, dermatologic

Conclusions

- Infants (esp. newborns) may have reduced capacity to eliminate drugs
- Anticipate the effects of ontogeny on drug disposition based on route of elimination
- More systematic pharmacokinetic studies of drugs in infants are needed
- Tissue sensitivity to the toxic effects of drugs may be age-dependent

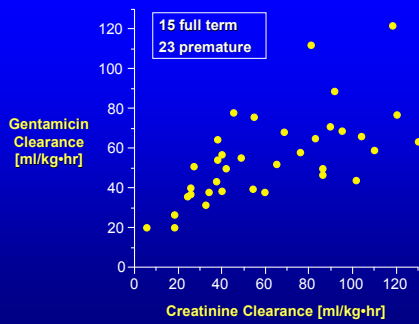


Cytochrome P450 Enzymes

PRESENT IN FETUS	APPEAR AFTER BIRTH	APPEAR 3-4 MONTHS OF AGE
CYP3A7*	CYP2D6	CYP1A2
CYP1A1	CYP3A4*	
CYP3A5	CYP2C9	
	CYP2C18/19	
	CYP2E1	

* Most abundant form

Gentamicin in the Newborn



Koren et al., Clin Pharmacol Ther 38:680-5, 1985
